REMARKS

Claims 1 and 2 have been cancelled without prejudice to the filing of continuing applications. Claims 3 and 4 have been amended to reflect dependency from claim 5. Claim 5 has been amended to limit its scope to treatment of Alzheimer's disease. No new matter is added herein.

35 U.S.C. § 112, first paragraph, Rejection

Claims 1-4, 6, and 20 stand rejected for lack of enablement for "preventing" Alzheimer's disease. Claim 5 has been amended to remove the words "or prevention." Reconsideration and withdrawal of this rejection are respectfully requested.

35 U.S.C. § 103(a) Rejections

Claims 1-3, 5, 6, 22, 23, and 25-30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Amouyel et al. (Annals of New York Academy of Sciences, 903, 437-441, 2000) in view of U.S. Patent No. 5,641,778 (Maibaum et al.). The applicants respectfully disagree. The claims are not rendered obvious by Amouyel et al. or Maibaum et al., taken alone or in combination.

Maibaum et al. discloses the compounds of the claims and indicates that they have biological activity as renin

inhibitors, and that they can therefore be used as anti-hypertensive agents. Maibum et al. make no mention at all that the compounds may be used in the treatment of Alzheimer's disease or any other neurological disorder.

The Examiner has pointed to Amouyel et al. for its teaching of the presence of certain components of the renin angiotensin system ("RAS") in the central nervous system ("CNS"). With respect to Amouyel et al. the Examiner specifically states:

> "Brain angiotensin levels influence cognitive processing acquisition and recall of newly learned tasks. Increased levels of angiotensin II induce an inhibitor influence on acquisiton by reducing acetylcholine release, this reduction in central cholinergic function is deleterious to cognitive functions. ACE (Angiotensin converting enzyme) inhibitors which inhibit angiotensin II synthesis will remove inhibitory influence on acetylcholine release (Page 439, 2" paragraph, lines 1-1 0). Renin controls conversion of Angiotensinogen to Angiotensin I and ACE is involved in conversion of Angiotensin I to Angiotensin II (Page 438, Figure 1). As rennin [sic] inhibitors reduce the levels of angiotensin I, there will not be enough angiotensin I for ACE to act on. Thus renin inhibitors improve cognitive function (Page 439, 2" paragraph, lines 1-10). However Amouyel et al teachings are silent about compounds."

The Examiner asserts that administration of a renin inhibitor results in improved cognitive function and points to the second paragraph of page 439 (believed by Applicants to be the first full paragraph of page 439) to support this assertion. The reference does not say this, however. Amouyel et al.

discusses a prior study of the administration of an ACE inhibitor and notes that such administration resulted in "improved cognitive function." The referenced paragraph makes no mention of renin inhibition. Nevertheless, the Examiner then concludes that the disclosure in Maibaum et al. that the compounds of the claims are renin inhibitors, when considered with the Amouyel et al. teachings, renders the claims obvious because Amouyel et al. suggests that the compounds would improve cognitive function. This conclusion is not supported by the references.

The Examiner's statement that "renin inhibitors improve cognitive function" is incorrect, and amounts to an overstatement of what Amouyel et al. actually teaches. The passages referred to by the Examiner from Amouyel only indicate that ACE inhibitor administration resulted in improved cognitive function. The reference includes no data clearly correlating inhibition of the enzyme to the improvement in cognitive function. Thus, there is no reason to believe that renin inhibition would generate similar results. It is entirely possible that the improvement in cognitive function was the result of the compound tested operating via some other mechanism, a mechanism unrelated to the RAS.

Applicants have attached another reference that pertains to components of the RAS, Neurobiology of Aging, 22, 541-46, 2001 (Savaskan et al.), but that was published after Amouyel et al. This reference is also listed on the enclosed PTO Form 1449. Like Amouyel et al., Savaskan et al. teaches that the mammalian brain contains detectable angiotensin converting enzyme (ACE) and Angiotensin II and their receptors. This reference, however, casts doubt on whether renin inhibition would impact cognitive function.

Savaskan et al. mentions that Angiotensin II inhibits acetylcholine release. That reference also notes that increased ACE activity MAY be responsible for cognitive impairment in AD (page 544, column 2, first full paragraph). The authors conclude that "this MAY explain the behavioral eliciting effects of ACE inhibitors on passive avoidance and retention performance [emphasis added].

The same paragraph on page 544 continues with the following additional conjectures:

> "An additional effect of ACE in cortex MAY be based on neuropeptide regulation, since ACE is involved in the degradation of several neuropeptides such as bradykinin, encephalins, substance P and neurotensin. The increase in ACE immunoreactivity in AD, which was accompanied by angiotensin II increase in some control, but all AD cases, MAY reflect the enhanced RAS activity in the disease progress [emphasis added].

It is clear that the mechanism behind any cognitive improvement with administration of an ACE inhibitor cannot positively be tied to the RAS system.

It is also important to note that neither Amouyel et al. nor Savaskan et al. states that the proteolytic kidney enzyme renin, or the compounds angiotensinogen or angiotensin I are found in the mammalian brain. Neither reference suggests or even speculates that inhibition of renin would affect cognitive function. The focus of these articles is ACE and, as indicated above, ACE in the cortex could affect numerous neuropeptides.

The Amouyel et al. and Savaskan et al. references do not provide the requisite reasonable expectation of success. Nothing can be predicted from these references about the use of a renin inhibitor for treatment of Alzheimer's disease.

Consequently, those skilled in the pertinent art at the time the invention was made would not have considered Amouyel et al. (or Savaskan et al.) to suggest that renin inhibitors such as those disclosed by Maibaum et al. would be useful in the treatment of Alzheimer's disease.

Reconsideration and withdrawal of the §103 (a) rejection based on Amouyel et al. and Maibaum et al. is respectfully requested.

Claims 4 and 20 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Amouyel et al. and Maibaum et al. further in view of U.S. Patent No. 5,063,208 (Rosenberg et al.) and U.S. Published Patent Application No. 20030114373 (Chen et al.). Applicants respectfully disagree. Because claims 4 and 20 depend from claim 5, and that claim is not rendered obvious by Amouyel et al. and Maibaum et al. for the reasons mentioned above, claims 4 and 20 are also not obvious. The Rosenberg and Chen references do not cure the deficiencies in the Amouyel et al. and Maibaum et al. references. Assuming, *arguendo*, that Amouyel et al. and Maibaum et al. did render obvious claims 1-3, 5, 6, 22, 23, and 25-30, the Rosenberg and Chen references in combination with Amouyel and Maibaum still do not render claims 4 and 20 obvious. Withdrawal of the rejection based on Amouyel et al. and Maibaum et al. in view of Rosenberg et al. and Chen et al. is respectfully solicited.

CONCLUSION

Applicants respectfully submit that all requirements of patentability have been met. Allowance of the claims and passage of the case to issue are therefore respectfully solicited.

Should the Examiner believe that a discussion of this matter would be helpful, the Examiner is invited to telephone the undersigned at (312) 913-0001.

Respectfully submitted,

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